

Sildenafil: a novel therapy in the management of cardiac syndrome X

Jamal N Khan, Nilan Patel, Rick Steeds, Chetan Varma

Cardiac syndrome X (CSX) is characterised by anginal pain in the presence of positive myocardial stress-testing but normal vessels on coronary angiography. Driven by dysfunction of the coronary microvasculature ('small vessel angina'), prognosis is usually excellent, but symptoms can be limiting. Management is aimed at symptom control and is based on standard anti-anginal drugs.^{1,2}

Case report

A 42-year-old man was limited by daily, exertional, anginal chest pains for 6 months. Symptoms could also occur during rest. He was a non-smoker and generally well, with mild hypercholesterolaemia (total cholesterol 6.4 mmol/L). Exercise ECG testing replicated his chest pain at 7 minutes on a standardised Bruce protocol with ECG changes diagnostic for ischaemia.

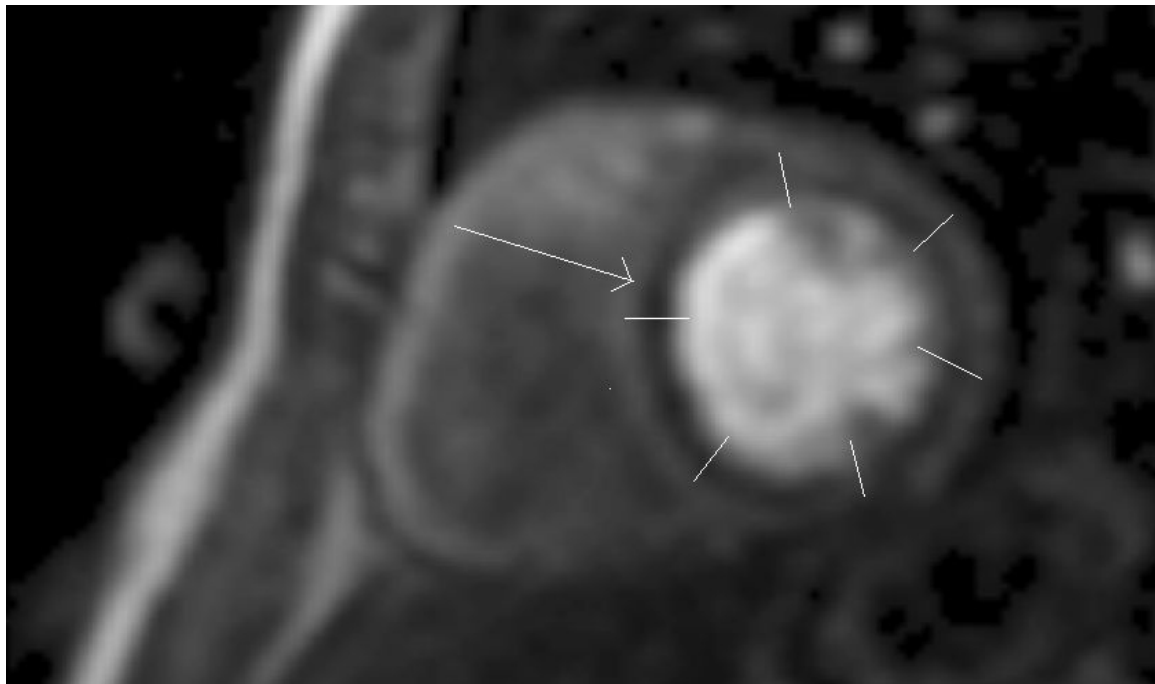
Subsequent coronary angiography revealed normal epicardial coronary vessels. He was further investigated with adenosine stress-perfusion cardiac magnetic resonance imaging (CMR) which showed diffuse subendocardial hypoperfusion, suggesting a diagnosis of cardiac syndrome X (Figure 1).

The image was obtained during the last minute of a 4-minute adenosine infusion (140 µg/kg/min) with a saturation prepared single shot fast spoiled gradient echo pulse sequence. This image is a short-axis view of the left ventricle (arrow at 9 o'clock positioned over septum, clockwise from this point are the six segment separated by white markers: anterior septum, anterior wall, lateral wall, posterior wall, inferior wall and inferior septum). The dark rim around the left ventricle demonstrates subendocardial ischaemia.

Sequential attempts to control symptoms using conventional anti-anginal drugs (long-acting nitrates, calcium-channel inhibitors, beta-blockers, and nicorandil) failed due to his intolerance to these medications, primarily citing headaches. A novel approach of 25 mg sildenafil daily was tried. This vastly improved his chest pain symptoms without side effects.

At 3 years follow-up, he remains stable with an extremely low symptom burden (less than three episodes per year). On occasions he has tried to discontinue therapy which has led to recurrence of symptoms. This raises the possibility of using sildenafil for the treatment of cardiac syndrome X (CSX).

Figure 1. Diffuse subendocardial hypoperfusion (arrow) persisting more than 5 cycles post appearance of gadolinium contrast within the LV myocardium in the short axis using a 1.5T whole body MRI scanner*



*Magnetom Sonata, Siemens, Erlangen, Germany. The image was obtained during the last minute of a 4 minute adenosine infusion (140 µg/kg/min) with a saturation prepared single shot fast spoiled gradient echo pulse sequence. This image is a short-axis view of the left ventricle (arrow at 9 o'clock positioned over septum, clockwise from this point are the six segment separated by white markers: anterior septum, anterior wall, lateral wall, posterior wall, inferior wall and inferior septum). The dark rim around the left ventricle demonstrates subendocardial ischaemia.

Discussion

The diagnosis of CSX can be aided using stress-perfusion CMR, which as shown by Panting and colleagues demonstrates diffuse subendocardial hypoperfusion during intravenous administration of adenosine (Figure 1). This supports the notion that CSX is ischaemic in origin¹.

It has been suggested that myocardial ischaemia in CSX results from dysfunctional small coronary arteries not visible at angiography, described as 'microvascular angina'.

Mosseri and colleagues demonstrated that endomyocardial biopsies show luminal narrowing and fibromuscular thickening in vessels under 1mm in diameter in CSX.² Functional abnormalities of the coronary microvasculature have also been demonstrated.

Piatti and colleagues reported that patients with CSX have a blunted nitric oxide (NO•) response and endothelin-1 inhibition to insulin, suggesting defective endothelium-dependent dilatation.³ Therefore both anatomical and functional abnormalities exist in CSX.

Phosphodiesterase-5 enzymes are found in most vascular beds and by causing their inhibition, NO• driven cyclic guanosine-monophosphate breakdown is reduced, resulting in potent vasodilatation.⁴ Sildenafil, a PDE-5 inhibitor is a vasoactive drug developed for the treatment of erectile-dysfunction also used in the management of pulmonary hypertension and Raynaud's phenomenon.

Adverse cardiac effects have been reported in patients with ischaemic heart disease using sildenafil for erectile-dysfunction. These include myocardial infarction, arrhythmias, and hypotension. These concerns have been questioned, suggesting that these adverse events may instead stem from the cardiac demands of sexual activity, the health of the population for whom sildenafil is prescribed, and adverse interaction with nitrates. Indeed, Arruda-Olson and colleagues demonstrated that in patients with stable coronary artery disease who were not taking nitrates, sildenafil did not potentiate myocardial ischemia.⁵

Our case is the first to demonstrate the effectiveness of sildenafil in treating CSX. It could potentially counter the functional defects noted within the coronary microvasculature. It may have a future role in managing CSX.

Author information: Jamal N Khan, Specialist Registrar in Cardiology; Nilan Patel, Specialist Registrar in Cardiology; Rick Steeds, Consultant Cardiologist; Chetan Varma, Consultant Cardiologist; Department of Cardiology, City Hospital, Birmingham, England

Correspondence: Dr Jamal Khan, Specialist Registrar in Cardiology, Department of Cardiology, City Hospital, Dudley Rd, Birmingham, B18 7QH, England, UK. Fax: +44 (0)121 5075649; email: jk211@le.ac.uk

References:

1. Panting JR, Gatehouse PD, Yang G-Z, et al. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. *NEJM*. 2002;346:1948–1953.
2. Mosseri M, Schaper J, Admon D. Coronary capillaries in patients with congestive cardiomyopathy or angina pectoris with patent main coronary arteries – ultrastructural morphometry of endomyocardial biopsy samples. *Circ*. 1991;84:203–210
3. Piatti P, Fragasso G, Monti LD, et al. Endothelial and metabolic characteristics of patients with angina and angiographically normal coronary arteries comparison with subjects with insulin resistance syndrome and normal controls. *JACC*. 1999;34:1452–60
4. Fries R, Shariat K, Von Wilmowsky H, Bohm M. Sildenafil in the treatment of Raynaud's phenomenon resistant to vasodilator therapy. *Circ*. 2005;112:2980-2985.
5. Arruda-Olson AM, Mahoney DW, Nehra A, et al. Cardiovascular effects of sildenafil during exercise in men with known or probable coronary artery disease: a randomized crossover trial. *JAMA*. 2002;287:719-725.